

### REMARKS/ARGUMENTS

Claims 21-35 are pending, claims 25-35 having been withdrawn from consideration. By this Amendment, claim 21 is amended. Support for the amendments to claim 21 can be found, for example, in the present specification at page 23, lines 16 to 21, and in previously presented claim 21. No new matter is added. In view of the foregoing amendments and following remarks, reconsideration and allowance are respectfully requested.

#### Withdrawn Claims

For the reasons set forth below, Applicants submit that all pending claims presently subject to examination are in condition for allowance. Because the withdrawn claims depend from, and thus recite all features of, allowable claim 21, rejoinder and allowance of the withdrawn claims are respectfully requested.

#### Rejection Under 35 U.S.C. §103

The Office Action rejects claims 21-24 under 35 U.S.C. §103(a) over U.S. Patent Application Publication No. US 2002/0047058 to Verhoff et al. ("Verhoff") in view of U.S. Patent No. 6,753,330 to Takano et al. ("Takano"). Applicants respectfully traverse the rejection.

Claim 21 recites "[a] composition, comprising: an extremely poorly water-soluble drug; and a porous silica material; wherein: the composition is obtained by treating a mixture comprising the porous silica material and the extremely poorly water-soluble drug with a supercritical fluid or subcritical fluid of carbon dioxide; the extremely poorly water-soluble drug has a solubility in water at 25 °C of less than 10 µg/mL prior to treatment; the porous silica material has an average pore diameter of from 1 to 20 nm, a total pore volume of pores having diameters within ±40% of the average pore diameter accounts for at least 60% of a

volume of all pores of the porous silica material, and the porous silica material has an X-ray diffraction pattern including at least one peak at a position of a diffraction angle ( $2\theta$ ) corresponding to a  $d$  value of at least 1 nm; and the composition is suitable for oral administration" (emphasis added). Verhoff and Takano do not disclose or suggest such a composition.

Applicants again submit that claim 21 distinguishes over Verhoff for at least the reasons discussed in the March 17, 2010 Amendment. However, Applicants provide the following further comments in view of the March 31, 2010 Advisory Action.

The Advisory Action asserts that Verhoff discloses using porous silica as milling media bodies at paragraphs [0140] to [0143]. *See* Advisory Action, page 2. Applicants submit that this is a misreading of Verhoff. In paragraphs [0140] and [0141], Verhoff describes inorganic materials that form the core of a polymer-coated particle. Verhoff further discloses that, after the polymer-coated particle is formed, the polymer coating can be subjected to processes that leave the coating "roughened or ridged or made porous." *See* Verhoff, paragraph [0143]. Accordingly, the passage of Verhoff identified in the Advisory Action does not disclose a porous silica material at all, but instead discloses a porous polymer coating. The description of polymer-coated particles at paragraphs [0140] to [0143] of Verhoff would not have led a skilled artisan to the porous silica material of claim 21.

Verhoff appears to contemplate using porous inorganic materials in combination with nonporous inorganic materials as milling media bodies. *See* Verhoff, paragraph [0110]. However, Verhoff also indicates that "porous media bodies are less tough than non-porous media bodies of the same composition," and thus a skilled artisan would not have been led to select such porous media bodies, in particular, instead of the clearly favored nonporous milling media bodies. *See* Verhoff, paragraph [0110]. Moreover, Verhoff provides absolutely no guidance regarding the characteristics of such porous media bodies. Claim 21

requires that the porous silica material has an average pore diameter of from 1 to 20 nm, a total pore volume of pores having diameters within  $\pm 40\%$  of the average pore diameter accounts for at least 60% of a volume of all pores of the porous silica material, and an X-ray diffraction pattern including at least one peak at a position of a diffraction angle ( $2\theta$ ) corresponding to a  $d$  value of at least 1 nm. Even if one of ordinary skill in the art were led to use a porous material by Verhoff, there is absolutely nothing in Verhoff that would have led a skilled artisan to a porous silica material having the particular characteristics recited in claim 21. *See, e.g.*, MPEP §2144.05.II.B (citing *In re Antonie*, 195 U.S.P.Q. 6 (C.C.P.A. 1977)) (particular parameter must first be recognized as result-effective variable before determination of workable ranges can be said to be obvious variation).

Verhoff discloses a method based on the application of mechanical energy to mill a solid substrate, such as an extremely poorly water-soluble drug. *See Verhoff*, paragraph [0098]. That is, mechanical energy is applied to cause collisions between milling media bodies and the drug, which mills the drug into finer particles and improves dissolution of the drug. *See Verhoff*, paragraph [0102]. There is nothing in Verhoff relating to the idea of improving dissolution of an extremely poorly water-soluble drug by allowing the drug to be adsorbed into pores of inorganic porous materials, such as the porous silica material of claim 21, by treatment with a supercritical or subcritical carbon dioxide fluid. Thus, even if Verhoff separately discloses aspects of composition of claim 21, there is nothing in Verhoff that would have led a skilled artisan to combine those aspects as would be required to obtain the composition of claim 21. *See Ex parte Whalen*, 89 USPQ2d 1078, 1084 (Bd. Pat. App. & Int. 2008) ("[t]he *KSR* Court noted that obviousness cannot be proven merely by showing that the elements of a claimed device were known in the prior art; it must be shown that those of ordinary skill in the art would have had some 'apparent reason to combine the known elements in the fashion claimed' ").

As indicated above, claim 21 is amended to require that the composition is suitable for oral administration. The composition of claim 21 is obtained by treating a mixture including a porous silica material and an extremely poorly water-soluble drug with a supercritical or subcritical carbon dioxide fluid. This treatment allows the extremely poorly water-soluble drug to dissolve in the carbon dioxide fluid and be adsorbed into the pores of the porous silica material. Upon dissolution and adsorption, the drug takes on an amorphous form, which changes properties of the drug, including increasing its solubility. Using supercritical or subcritical carbon dioxide as a fluid is important to provide a composition suitable for oral administration, as now required by claim 21. Using an organic solvent, such as chloroform, to dissolve the extremely poorly water-soluble drug instead of the carbon dioxide fluid would not be desirable in preparation of a composition for oral administration because some organic solvent may remain in the resulting composition even after removing the organic solvent by drying. By contrast, carbon dioxide does not remain in a composition as in claim 21 because of carbon dioxide vaporizes – a drying step is not required. Further, even if carbon dioxide remains in the composition, trace amounts are safe in compositions for oral administration. The combination of features in claim 21 provides clear benefits. There is nothing in Verhoff that would have led a skilled artisan to such combination.

For the reasons discussed above, Verhoff fails to disclose or suggest each and every feature of claim 21. Takano does not remedy the deficiencies of Verhoff. Takano is cited for its alleged disclosure of a pharmaceutical solid dispersions including 2-benzyl-5-(4-chlorophenyl)-6-[4-(methylthio)phenyl]-2H-pyridazin-3-one. See Office Action, pages 6 to 7. However, Takano, like Verhoff fails to disclose or suggest a composition including a porous silica material as recited in claim 21. Accordingly, the combination of references fails to disclose or suggest each and every feature of claim 21.

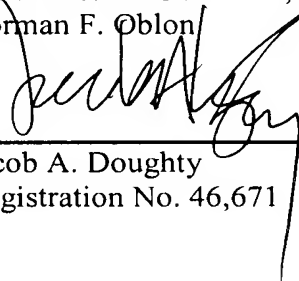
As explained, claim 21 would not have been rendered obvious by Verhoff and Takano. Claims 22-24 depend from claim 21 and, thus, also would not have been rendered obvious by Verhoff and Takano. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

Conclusion

For the foregoing reasons, Applicants submit that claims 21-35 are in condition for allowance. Prompt reconsideration and allowance are respectfully requested.

Respectfully submitted,

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